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In-Process Control Measures for Management of Non-Chronic Diseases in Plasma Fractionation: Parvovirus B19

Introduction

Since January 2002, the major producers of plasma-derived therapies in the United States have voluntarily instituted in-process control measures to help prevent the transmission of Parvovirus B19 through fractionated therapies. Although Parvovirus B19 infection causes a relatively benign disease with widespread prevalence, control measures directed at reducing the potential for Parvovirus B19 transmission have been instituted to further assure the safety of plasma-derived therapies. The in-process control measures currently in place consist of various testing protocols and inventory management techniques aimed at assuring low levels of Parvovirus B19 in the manufacturing pool; they are not intended as a donor screening mechanism.

In-process control measures are an appropriate means of increasing the margin of safety for plasma-derived therapies while retaining the desirable protective antibodies against Parvovirus B19 infection. However, such measures are not an appropriate donor screening mechanism, nor is such an approach warranted for non-chronic diseases such as Parvovirus B19. As discussed later in this paper, there is no public health benefit to be achieved through identification and notification of donors with high titer Parvovirus B19 donations.

Unlike chronic, life-threatening diseases such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), donor notification of Parvovirus B19 infection confers no health benefit to donors in the plasma donation setting and indeed, may cause undue concern and confusion. This is because most Parvovirus B19 infections are asymptomatic and high viremia typically persists only for two weeks. Given this short period of viremia and the limited potential to impact the clinical course of the typically mild disease, in-process control measures are the most appropriate means for addressing Parvovirus B19.

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Epidemiology of Parvovirus B19

Human populations are widely exposed to non-chronic viruses such as Parvovirus B 19. Parvovirus B19 is an acute, self-limiting disease without chronic sequelae in normal individuals. It is a common cause of human infections worldwide and is normally spread via the respiratory route. The most common presentation of Parvovirus B19 infection is erythema infectiosum. Approximately 50% of children aged 15 are seropositive, a prevalence that rises to more than 90% in the elderly (Edwards et al., 1981, Brown et al. 1994). Infections in temperate climates are more frequent in late winter to early summer, and the rate of infection may increase in a cyclic manner every three to five years. Importantly, most infections are asymptomatic.

The prevalence and incidence of Parvovirus B19 infections in blood/plasma donors are analogous to the normal population. Serological studies have shown that approximately 50% or more of the donor population have neutralizing antibodies against Parvovirus B19 and approximately 1:20,000 to 1:40,000 donations during non-epidemic seasons will contain high titres of Parvovirus B19 (Cohen et al., 1990. J. Virol. Methods; 30:233-238). In an epidemic season up to 1:167 blood donations and in the non-epidemic season between 1:3,300 to $\geq$ 1:6,000 donations contained NAT- detectable Parvovirus B19 DNA (Prowse et al., 1997. Vox. Sang. 72: 1-10).

Antibodies to Parvovirus B19 are produced following infection, conferring protective immunity. The presence of Parvovirus B19 specific IgG signifies a past infection only, whereas the presence of IgM and/or virus DNA is indicative of a recent infection. In acute Parvovirus B 19 infections, viremia levels as high as 10^{12} to 10^{14} virus particles per milliliter of serum may be detected over a period of one to two days (Kurtzman et al., 1989).

Parvovirus B19 infections typically resolve with the appearance of neutralizing antibodies, starting about 5 days post infection for IgM and about 7 days post infection for IgG. The appearance of antibodies coincides with disappearance of virus from the circulation. As such, the period of high viremia lasts approximately 2 weeks. In some cases it has been observed that individuals with low level viremia continue to produce Parvovirus B19 for a longer period of time. However, chronic carriers have not been identified.

Safeguards for Chronic and Non-Chronic Diseases

Each of the major producers of plasma-derived therapies has instituted validated viral inactivation and removal measures for the three viruses of major public health import: hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Since the implementation of these inactivation and removal measures, there has

been no reported case of HBV, HCV or HIV transmission via plasma therapies (Tabor E, Transfusion 1999, Nov – Dec; 39 (11 –12) 1160-68). The health risk associated with these chronic, life-threatening diseases now appears to be adequately managed for plasma therapies.

Additional safeguards for both chronic and non-chronic diseases have been put in place through the PPTA voluntary standards programs such as Quality Standards of Excellence, Assurance and Leadership (QSEAL). The QSEAL program has five standards:

- Qualified Donor
- Inventory Hold
- Viral Marker Standard
- Nucleic Acid Amplification Technology (NAT) testing for HIV, HBV, and HCV
- Parvovirus B19 In-Process Control Limit

A brief summary of the relevant standards is provided below.

The Parvovirus B19 In-Process Control Limit standard was implemented to minimize the potential for the transmission of Parvovirus B19 through plasma derived therapies. Under this standard, companies have validated their individual NAT based in-process control systems to assure that high levels of Parvovirus B19 are not present in plasma manufacturing pools. This in-process control of the Parvovirus B19 level in a manufacturing pool provides a greater assurance of the safety of manufactured plasma therapies vis-à-vis Parvovirus B19.

The current control limit in the manufacturing pool for Parvovirus B19 is not more than 10^5 IU per mL. While the QSEAL control limit control limit assures that no manufacturing pool will contain more than 10^5 IU per mL, the Parvovirus B19 levels in actual manufacturing pools are usually substantially lower than this limit. Recent Parvovirus B19 quantitative NAT test data on manufacturing pools using the 10^5 IU per mL standard showed Parvovirus B19 levels ranging from 10^2 – $10^{2.7}$ IU per mL. These lower actual Parvovirus B19 titers are due to the robust design of the test system and the resulting detection and removal of moderately titered Parvovirus B19 plasma.

Moreover, viral inactivation methods validated for enveloped viruses such as HBV, HCV and HIV have been shown to reduce levels of non-enveloped viruses such as Parvovirus B19. Consequently, the industry standard control limit of 10^5 IU of Parvovirus B19 per mL for manufacturing pools actuality results in much lower levels once viral inactivation methods are applied. A further reduction in the standard control

limit may have the unintended consequence of excluding donations that have high levels of beneficial Parvovirus B19 antibody.

Under the Qualified Donor standard, plasma intended for fractionation can be collected only from individuals who have demonstrated a commitment to the process through completion of two full health and screening procedure, including serology and NAT testing for the three major chronic viruses (HBV, HCV, HIV). The Inventory Hold standard requires that each donation be held for a minimum period of 60 days prior to pooling or manufacture. This permits the retrieval of donations from individuals who subsequently test positive for a chronic virus or about whom some adverse post donation information is learned.

Under the NAT standard manufacturers must implement NAT testing for every donation as a donor screening mechanism for HBV, HCV and HIV. Using the NAT methodology, it is possible to detect infectious individuals sooner and prevent the possibility of a potentially infectious but undetected donation from entering a manufacturing pool. In addition, NAT testing helps realize the public health benefit to be achieved through early detection, notification and treatment for individuals infected with these chronic diseases.

Rationale for In-Process Control Measures

In-process control measures can be defined as a set of testing protocols and inventory management techniques designed to reduce the potential for non-chronic disease transmission by preventing high titer donations from entering the manufacturing plasma pool. Although specific testing protocols and inventory management techniques for Parvovirus B19 vary from company to company, they achieve the same goal: eliminating plasma with high titers of Parvovirus B19 from the plasma pools used to produce plasma derived therapies. To a greater extent than for chronic diseases where the focus is on individual donors and donations, the focus of in-process control measures for non-chronic diseases is the management of the manufacturing pool. Accordingly, donor identification and notification are not part of the in-process control methods used to manage Parvovirus B19 titers in manufacturing pools.

In-process control measures for Parvovirus B19 include the use of NAT testing algorithms. Like NAT testing for chronic diseases, NAT testing for Parvovirus B19 involves the utilization of sample minipool matrices. A reactive result from a minipool permits the identification of subsets (e.g., rows and columns) of plasma units in which the reactive unit exists. In this scenario, some companies may trace back to the single infectious plasma unit while others may identify a group of units in which the infectious unit exists. In either case, manufacturers eliminate these high titer plasma units from the manufacturing pool.

In-process control measures do not constitute a medical diagnostic test or donor screening method because not all reactive donations are discarded as part of the in-process control methodology. As noted above, the industry standard control limit for Parvovirus B19 in a manufacturing pool is not more than 10^5 IU per mL. This limit is appropriate to minimize the likelihood of Parvovirus B19 transmission through plasma derived therapies while at the same time assuring the presence of adequate antibody titers against Parvovirus B-19 required for immune globulin preparations. Nonetheless, using this control limit means that some individual units with Parvovirus B19 titers below 10^6 IU per mL remain undetected.

Additionally, in some circumstances non-reactive plasma units may be discarded as a result of the in-process control approach to managing non-chronic diseases. Although specific practices vary from company to company, each company has optimized its internal process control steps to maximize the opportunities for eliminating high titer plasma from production pools. At the same time, companies strive to maximize the utilization of suitable plasma without unnecessarily discarding otherwise acceptable donations. Consequently, the industry has instituted in-process control methods that allow for flexibility in the specific strategies employed to achieve the objective of managing the titers of Parvovirus B19 in manufacturing pools.

Public Health Considerations for Non-Chronic Diseases

Non-chronic diseases present public health considerations that are different from those of chronic, life threatening diseases such as HBV, HCV and HIV. For chronic diseases, identification and notification of infected individuals is a public health imperative. However, this public health imperative stands in contradistinction to non-chronic conditions that have little public health impact.

Non-chronic viruses are acute and self-limiting in normal individuals. Moreover, individuals who contract Parvovirus B19 typically are asymptomatic and develop a life-long immunity within two weeks of infection. More significant sequelae are rare and usually occur only in particularly susceptible populations with preexisting conditions. Many of the conditions that could result in more significant disease also would be a basis for rejecting a potential donor from a susceptible population during routine health screening. Thus, the rationale for donor notification is obviated by the fact that such individuals would likely be deferred from donating plasma.

Furthermore, no meaningful opportunity would exist to provide donor notification. Even assuming some public health benefit could be gained by donor notification, in-process control protocols require between 25 to 60 days for the identification of an individual high titer Parvovirus B19 donation. As a consequence, an infected normal donor would have already cleared the virus and developed sufficient antibodies to confer a life-long

immunity by the time notification occurred. Any medical information provided to the donor at this time would not be actionable. Given these circumstances, the psychological impact of donor notification must be weighed against the immateriality of the information presented.

Indeed, it may be considered unethical to notify a donor of non-actionable medical information that will increase anxiety, fear, or concern, and result in no potential medical benefit. Donor notification of a positive Parvovirus B19 test result would have to occur in the same setting where other donors are notified of a reactive test result for life threatening diseases such as HBV, HCV and HIV. For persons with no medical or scientific background it can be difficult to clearly distinguish between non-chronic viruses such as Parvovirus B19 and more significant, life altering conditions such as HIV/AIDS. Donor notification in these circumstances would likely do more harm than good.

Conclusion

Through the establishment of voluntary industry standards, the plasma fractionation industry has instituted in-process control measures that effectively minimize the potential for the transmission of Parvovirus B19. The methodologies utilized to address non-chronic viruses such as Parvovirus B19 are different than those established to address chronic and potentially life-threatening diseases such has HBV, HCV and HIV. For non-chronic viruses, donor identification and notification are not warranted due to the low public health impact of such diseases and the lack of opportunity to meaningfully impact the course of clinical illness in individuals infected with the disease.

The objective of in-process control measures is to strike a balance between the elimination of plasma that may transmit virus and the retention of sufficient protective antibodies so that immune globulin preparations remain efficacious. Manufacturers of plasma therapies also must be given enough flexibility in the design of their in-process control steps to allow for the optimal use of available plasma for the production of therapies. The PPTA voluntary standard provides flexibility in achieving the established in-process control limit to minimize the potential for transmission of Parvovirus B19. The plasma fractionation industry has again demonstrated its commitment to provide a safe and stable supply of plasma derived therapies.